Articles

Mortality in relation to oral contraceptive use and cigarette smoking

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Summary

Background As part of the Oxford Family Planning Association study, we compared mortality in relation to oral contraceptive use and smoking to highlight the differences between them from the perspective of public health.

Methods The study consisted of 17 032 women, aged 25–39 years at entry, recruited between May 1, 1968, and July 31, 1974, who had used oral contraceptives, a diaphragm, or an intrauterine device. We assessed mortality from follow-up data recorded until Dec 31, 2000. The analysis is based on woman-years of observation.

Findings We analysed 889 deaths. Women who had ever used oral contraceptives had increased mortality from cervical cancer (rate ratio 7·2, 95% CI 1·1–303), and decreased mortality from other uterine (0·2, 0·0–0·8) and ovarian cancers (0·4, 0·2–0·7). Oral contraceptives had some adverse effect on deaths from ischaemic heart disease in women who smoked 15 or more cigarettes per day. For all causes of mortality, the rate ratio for death in women who ever used oral contraceptives was 0·89 (95% CI 0·77–1·02). By contrast, this rate ratio was 1·24 (1·03–1·49) in those who smoked one to 14 cigarettes per day, and 2·14 (1·81–2·53) in those who smoked 15 or more cigarettes per day.

Interpretation There was no harmful effect of oral contraceptive use on overall mortality. By contrast, death from all causes was more than twice as high in smokers of 15 or more cigarettes a day as in non-smokers. The harmful effect was already apparent in women aged 35–44 years.

Lancet 2003; **362:** 185–91

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Introduction

Patterns of mortality in the Oxford Family Planning Association (Oxford FPA) contraceptive investigation have been reported previously,[1–4] most recently in 1989,[4] by which time 238 women had died. We present our findings until Dec 31, 2000, based on analysis of 889 deaths. We examined mortality associated with oral contraceptive use and cigarette smoking. In our view, this issue is of public health importance because both use of such contraceptives and smoking are common in women of childbearing age and, arguably, at least as much negative publicity exists about oral contraceptive use as about smoking. Our results should enable direct comparisons between the two exposures that were analysed with information from the same database.

Methods

Study population

Methods used in the study have been described elsewhere.[1] 17 032 women were recruited from 17 family planning clinics in England and Scotland between Jan 1, 1968 and Dec 31, 1974. To be eligible, the women had to be aged 25–39 years, married, white, British, willing to cooperate, and have been a user of either the contraceptive pill for at least 5 months, or a diaphragm or an intrauterine device for at least 5 months without previous pill use. At recruitment, women were asked about their date of birth, child-bearing history, contraceptive history, height, weight, social class (based on husband's occupation), smoking habits, and medical history. The records of all participants were also flagged in the National Health Service (NHS) central registries in England and Scotland to obtain automatic notifications of death.

The causes of death reported here (8th edition of the International Classification of Disease codes in parentheses) were selected because of their relevance to oral contraceptive use or smoking. Causes included are breast cancer (174); cervical cancer (180); other uterine cancer (182); ovarian cancer (183); malignant melanoma (172); colorectal cancer (153–154); lung cancer (162); lymphatic and haemopoietic cancer (200–209); other cancers (140–239 less the above); ischaemic heart disease (410–414); subarachnoid and intracerebral haemorrhage (430–431); other cerebrovascular disease (432–438); other circulatory disease (390–458 less the above circulatory diseases); diseases of respiratory system (460–519); diseases of liver, gallbladder, and pancreas (570–577); accidents and violence (800–999); all other causes (001–999 less all the above).

The women were interviewed during follow-up clinic visits. They were asked about pregnancies and their outcome, changes in contraceptive practices, and referrals to hospital. When appropriate, they were also questioned about use of hormone replacement therapy (HRT) and menopausal status. Diagnoses after a hospital stay were

confirmed by discharge summaries and pathology reports. When necessary, women were sent a postal follow-up form and, if this was not returned, they were interviewed by telephone or at home. Work was coordinated by a research assistant in every clinic. Yearly contact was maintained with the participants until they were 45 years of age, with an annual loss to follow-up for non-cooperation or failure to trace of about 0·4%. MV did all diagnostic coding, to avoid inter-observer variation.

At age 45 years, every woman was allocated to one of three groups on the basis of oral contraceptive use: never used; used for 8 years or more; and used for less than 8 years. Only those in the first two groups were followed up yearly, which continued until mid-1994. This action at age 45 reduced the number of women under detailed follow-up and cut study costs. We reasoned that the contrast between non-users of oral contraceptives and long-term users was of greatest importance. We also recognised that most women would have stopped such contraception by age 45. Thus, assessment of the effects of use of oral contraceptives on death should be possible for the complete cohort of women, except for those who had emigrated.

Statistical analysis

The analysis is based on woman-years of observation. We analysed patterns of mortality for four categories of oral contraceptive use (never used, used 1–48 months, used 49–96 months, and used 97 months or more), and four categories of smoking habit at recruitment (never smoked, ex-smoker, smoked one to 14 cigarettes daily [light smoker], and smoked 15 or more cigarettes daily [heavy smoker]). We added exposure duration at recruitment and that of exposure periods during follow-up to calculate total duration of oral contraceptive use individually.

Possible confounding variables were examined and, where possible, those of importance were included in the analyses. Indirectly standardised mortality rates and rate ratios were calculated as described by Vessey and colleagues.[1] For significance tests and calculation of 95% CIs we used Breslow and Day's methods.[5]

Two-thirds of oral contraceptive exposures were from preparations containing 50 μg of oestrogen. This dose is now believed to be too high, and has been little used for two decades. For this reason, and in view of the small numbers of deaths in many of the disease categories, we did not analyse data by type of oral contraception.

Role of the funding source

This work has been funded by the Medical Research Council from its inception in 1968. Some support was also received in the 1980s from the Imperial Cancer Research Fund and the James Knott Family Trust. David Yeates receives funding from the research and development directorate of the Department of Health and Social Care (South). None of the institutions was involved with study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Results

Preliminary assessment of data

We first compared mortality from oral contraceptive use and that from smoking in women who were active in the study (ie, under individual yearly follow-up) with that in the whole cohort to the end of 2000. The active cohort analysis was based on woman-years of observation from recruitment until (a) emigration (802 women), death (384), or age 45 being reached with less than 8 years of pill use (6041); (b) loss to follow-up or withdrawal of cooperation (1208); or (c) the end of the individual data collection phase of the study (July 31, 1994) being reached (8597). The whole cohort analysis was based on woman-years of observation from recruitment to Dec 31, 2000, with the exclusion of those who died (889) or emigrated during the active phase (802). Mortality in relation to oral contraceptive use and smoking, in both overall and specific disease categories, was closely similar for both the active (384) and whole cohort (889). Accordingly, further analyses reported here are only for the whole cohort.

We considered age, parity, social class at entry, body-mass index at entry, smoking at entry (for oral contraceptive use analyses), duration of oral contraceptive use (for smoking analyses), hysterectomy, oophorectomy, age at menopause, and HRT to be potential confounding variables.

Assessment of the importance of the following variables was straightforward: age (5-year groups), parity (0, 1, 2, 3, ⩾4 births), social class at entry (1–2, 3, 4–5, and other [Registrar General's Classification]), and body-mass index at entry (<20, 20–21·9, 22–23·9, 24–25·9, 26–27·9, ⩾28 kg/m^2). We made this assessment by analysing oral contraceptive use, smoking, and mortality in relation to these variables. Examination of the possible confounding effect of oral contraceptive use in analyses of smoking and vice versa was also straight forward. Taking these analyses into account, we did the following: (1) adjusted for age, parity, social class, and smoking in all analyses to look for effects of oral contraceptives on mortality; (2) in analyses of the effects of such contraceptives on circulatory disease mortality, we also adjusted for body-mass index; (3) in all analyses of the effects of smoking on mortality we adjusted for age, parity, and social class; (4) in analyses of the effects of smoking on mortality from breast cancer and reproductive cancer, we also adjusted for total duration of oral contraceptive use; (5) in analyses of effects of smoking on mortality from circulatory disease, all the above mentioned variables were taken into account, together with body-mass index.

Information about hysterectomy, oophorectomy, age at menopause, and use of HRT was available only for women in the active cohort. Thus, we analysed the active cohort to see whether these variables might distort findings in whole cohort analyses. As expected, women who smoked generally had a slightly earlier age at menopause than other women. 16% of non-smokers had reached menopause by age 45 years, 50% by 50 years, and 87% by 55 years. Corresponding percentages for heavy smokers were 22%, 61%, and 88%, respectively. There was no important relation between smoking and the other three variables. Oral contraceptive use showed no important association with hysterectomy, oophorectomy, or age at menopause. HRT, however, was used a little more often by women who had taken oral contraceptives than by other women. In women who had never used these contraceptives, 17% used HRT for more than 2 years. The corresponding percentage for those who had used oral contraceptives for more than 8 years was 21%. We judged that this small difference would be unlikely to distort the analyses of the effects of oral contraceptives.

Woman-years of observation

889 deaths were noted during 479 400 woman-years of observation. Only 8% of the woman-years are for women aged 60 or more. 16% represent current or recent (within 1 year) oral contraceptive use, and 33% relate to women

	Total duration of oral contraceptive use (months)				Number of cigarettes smoked per day			
	Never used	⩽48	49–96	⩾97	Non-smoker	Ex-smoker	1–14	⩾15
Breast								
Number	83	29	40	42	118	27	24	25
RR	1·0	0·8 (0·5–1·2)	0·8 (0·6–1·2)	0·8 (0·5–1·2)	1·0	1·1 (0·7–1·7)	0·6 (0·4–1·0)	1·0 (0·6–1·5)
Uterine cervix								
Number	1	3	5	8	6	1	3	7
RR	1·0	5·3 (0·4–280)	6·3 (0·7–299)	9·1 (1·2–404)	1·0	0·8 (0·0–6·6)	1·1 (0·2–5·2)	2·6 (0·7–9·3)
Other uterine								
Number	8	2	0	0	6	1	2	1
RR	1·0	0·6 (0·1–2·9)	..	..	1·0	0·9 (0·0–7·4)	1·2 (0·1–6·5)	0·8 (0·0–6·9)
Ovary								
Number	36	17	3	5	39	4	13	5
RR	1·0	1·1 (0·6–2·0)	0·2 (0·0–0·5)	0·2 (0·1–0·6)	1·0	0·5 (0·1–1·3)	1·1 (0·6–2·2)	0·6 (0·2–1·5)

RR=rate ratio. 95% CIs are shown in parentheses. Oral contraceptive data were adjusted for age, parity, social class, and total duration of oral contraceptive use.

Table 1: **Mortality from breast, uterine, and ovarian cancer in relation to total duration of oral contraceptive use and number of cigarettes smoked per day at entry to the study**

who had not used such contraceptives in the preceding 96 months.

Deaths from breast and reproductive cancers

There was no gradient of risk between duration of oral contraceptive use and breast cancer mortality (table 1). The rate ratio comparing ever-users of oral contraceptives with never-users (not shown in table 1) was 0·8 (95% CI 0·6–1·1). Smoking and breast cancer mortality were not significantly associated. Death from cervical cancer was significantly related to oral contraceptive use; indeed there was only one death in the non-user group. The rate ratio comparing ever-users with never-users was 7·2 (1·1–303). Cervical cancer mortality also showed some relation with heavy smoking although the raised rate ratio in the heavy smoker group was not significant (table 1). There were ten deaths from other uterine cancers—four from endometrial cancer and six from sarcomas. There was a strong negative relation between mortality and oral contraceptive use. In a comparison of ever-users of oral contraceptives with never-users, the rate ratio was 0·2 (0·0–0·8). Mortality was unrelated to smoking. Ovarian cancer mortality was much lower in medium-term (49–96 months) and long-term (>96 months) oral contraceptive users than in non-users. The rate ratio comparing ever-users with never-users was 0·4 (0·2–0·7). In a separate analysis, oral contraceptive users who had not used the pill within the last 96 months had a significantly lower risk of death from ovarian cancer than never-users (rate ratio 0·5; 95% CI 0·3–0·9). There was no significant relationship between smoking and ovarian cancer.

Deaths from other cancers

There were 11 deaths from melanoma; although there were some raised rate ratios in both the oral contraceptive and the smoking analyses, none was significant (table 2). Likewise, there were no significant associations between oral contraceptive use or smoking and colorectal cancer mortality. All the rate ratios in the different smoking categories were nonetheless higher than 1.

We noted no significant relation between death from lung cancer and oral contraceptive use. The association between mortality from this cause and smoking was very strong. Mortality from cancers of the lymphatic and haemopoietic system showed no significant association with oral contraceptive use or smoking. When the other cancers were grouped together, mortality was not significantly related to oral contraceptive use. Comparison of ever-users with never-users gave a rate ratio of 0·8 (95% CI 0·5–1·1). We recorded a slight (not significant) positive association between heavy smoking and death from other cancers.

Deaths from cardiovascular disease

The risk of death from ischaemic heart disease was slightly (but not significantly) raised in all oral contraceptive user

	Total duration of oral contraceptive use (months)				Number of cigarettes smoked per day			
	Never used	⩽48	49–96	⩾97	Non-smoker	Ex-smoker	1–14	⩾15
Malignant melanoma								
Number	3	1	2	5	4	2	5	0
RR	1·0	0·8 (0·0–9·3)	1·1 (0·1–9·6)	2·5 (0·5–16·1)	1·0	2·3 (0·2–16·3)	3·7 (0·8–18·5)	..
Colorectal								
Number	18	7	11	10	21	7	10	8
RR	1·0	0·9 (0·3–2·3)	1·1 (0·5–2·5)	0·8 (0·4–1·9)	1·0	1·6 (0·6–3·9)	1·4 (0·6–3·2)	1·5 (0·6–3·6)
Lung								
Number	15	9	12	18	3	1	20	30
RR	1·0	1·4 (0·6–3·5)	1·2 (0·5–2·6)	1·3 (0·6–2·8)	1·0	1·6 (0·0–20·4)	19·9 (5·9–104)	38·1 (11·9–195)
Lymphatic haemopoietic								
Number	16	6	8	11	21	9	4	7
RR	1·0	0·9 (0·3–2·5)	1·0 (0·4–2·5)	1·2 (0·5–2·7)	1·0	2·0 (0·8–4·6)	0·6 (0·2–1·8)	1·4 (0·5–3·5)
All other cancers								
Number	54	20	19	33	68	10	21	27
RR	1·0	0·8 (0·5–1·4)	0·6 (0·3–1·0)	0·9 (0·6–1·4)	1·0	0·7 (0·3–1·4)	0·9 (0·5–1·5)	1·5 (0·9–2·4)

RR=rate ratio. 95% CIs are shown in parentheses. Oral contraceptive data were adjusted for age, parity, social class, and smoking. Smoking data were adjusted for age, parity, and social class.

Table 2: **Mortality from other cancers in relation to total duration of oral contraceptive use and number of cigarettes smoked per day at entry to the study**

	Total duration of oral contraceptive use (months)				Number of cigarettes smoked per day			
	Never used	≤48	49–96	≥97	Non-smoker	Ex-smoker	1–14	≥15
Ischaemic heart disease								
Number	20	12	22	18	20	4	17	31
RR	1·0	1·3 (0·6–2·7)	1·7 (0·9–3·3)	1·2 (0·6–2·4)	1·0	9 (0·2–2·7)	2·1 (1·0–4·2)	4·8(2·7–9·0)
Haemorrhagic stroke								
Number	7	8	6	7	8	3	5	12
RR	1·0	2·2 (0·7–7·1)	1·0 (0·3–3·4)	1·0 (0·3–3·4)	1·0	1·9 (0·3–7·9)	2·0 (0·3–7·9)	5·8 (2·2–16·5)
Other stroke								
Number	8	3	1	2	5	0	5	4
RR	1·0	1·0 (0·2–4·0)	0·2 (0·0–1·9)	0·5 (0·1–2·7)	1·0	..	2·9 (0·7–12·6)	4·3 (0·9–20·0)
All other circulatory disease								
Number	18	6	9	8	19	5	7	10
RR	1·0	0·9 (0·3–2·5)	0·9 (0·4–2·2)	0·7 (0·3–1·7)	1·0	1·3 (0·4–3·6)	1·2 (0·4–2·9)	1·9 (0·8–4·3)

RR=rate ratio. 95% CIs are shown in parentheses. Oral contraceptive data were adjusted for age, parity, social class, smoking, and body-mass index. Smoking data were adjusted for age, parity, social class, total duration of oral contraceptive use, and body-mass index.

Table 3: **Mortality from cardiovascular disease in relation to total duration of oral contraceptive and body mass index use (months) and number of cigarettes smoked per day at entry to the study**

categories (table 3). The rate ratio that compared ever-users with never-users was 1·4 (0·8–2·5). In a separate analysis, the rate ratio for women who were current or recent oral contraceptive users was 1·0 (0·2–3·5). Smoking had a substantial effect on mortality from ischaemic heart disease.

We also sought evidence for any interaction between oral contraceptive use and smoking on mortality from ischaemic heart disease. First, we grouped the mortality data into three smoking categories (never smoked, ex-smoker, and current smoker) and two categories of oral contraceptive use (never used and ever used). A test for heterogeneity in the rate ratios gave a p value of 0·032 (χ^2 test). In a more detailed analysis, there was no evidence of any effect of oral contraceptive use in non-smokers, ex-smokers, or light smokers. In heavy smokers, however, the rate ratios for oral contraceptive use for 48 months or less, 49–96 months, and 97 months or more, compared with non-use were 2·4 (0·4–16·3), 4·8 (1·3–26·2), and 2·8 (0·8–15·8), respectively. This pattern was seen in both current and recent users, and in past users.

Mortality from haemorrhagic stroke was higher (but not significantly so) in women using oral contraceptives for up to 48 months than in non-users. The rate ratio in ever-users in comparison with never-users was 1·3 (0·5–3·5). Analyses by recency of use showed no particular pattern. Smoking was strongly related to mortality from haemorrhagic stroke. An analysis of oral contraceptive effects within smoking categories did not show any indication of interaction (p=0·868).

Mortality from other stroke (including four deaths from thrombotic stroke) was not raised in oral contraceptive users; indeed the rate ratios in all user categories were below 1. When ever-users were compared with never-users the rate ratio was 0·6 (0·2–2·0). Analysis by recency of use showed no pattern. Smoking increased mortality from other stroke. We noted no evidence of an interaction between oral contraceptive use and smoking (p=0·156).

There were no significant associations between mortality from other circulatory disease and either oral contraceptive use or smoking although the rate ratio in heavy smokers was increased. There were ten deaths from venous thromboembolism (VTE) but all were in older women (age range 49–63) and three women had a history of cancer; six had used oral contraceptives in the past but none for many years before death. Three deaths were from mesenteric artery thrombosis. Two of these women had used oral contraceptives in the past, but one not for 24 years and the other not for 10 years.

Deaths from other causes

No significant association was recorded between oral contraceptive use and death from respiratory disease. Smoking, however, showed a strong relation with mortality from respiratory disease (table 4). Mortality from diseases of the liver, gallbladder, and pancreas was increased in two of the oral contraceptive use groups, but the differences were not significant. The rate ratio comparing ever-users with never-users was 1·8 (0·6–7·3). There was a strong relation between smoking and death from diseases of this group. Deaths from accidents and violence were unrelated to oral contraceptive use and smoking. Likewise, deaths from all other causes were not significantly related to oral contraceptive use or smoking, although the rate ratios in both light and heavy smokers were raised.

Deaths from all causes

Rate ratios in the three oral contraceptive use groups were all 1 or less (table 4). The rate ratio comparing ever-users with never-users was 0·89 (0·77–1·02). By contrast, overall mortality was strongly related to smoking; the rate ratio in the heavy smoker group was 2·14 (1·81–2·53). Excess mortality in heavy smokers in comparison with non-smokers was already apparent at ages 35–44 where it amounted to 0·7 deaths per 1000 woman-years (table 5). At ages 45–54 and 55 or older, the corresponding excess mortality figures are 2·0 and 4·9 deaths per 1000 woman-years, respectively.

Discussion

The present analysis is based on a much larger number of deaths (889) than those in our previous reports,[1–4] and considers mortality from smoking and from oral contraceptive use. Although many researchers have described the effects of smoking on mortality in women,[6] we are unaware of any who have compared the effects of smoking with those of oral contraceptive use on the basis of data derived from the same study. Furthermore, as far as we are aware, the findings presented here are the most extensive published so far about the effects of smoking on mortality in young and middle-aged British women.

The reliability of the Oxford FPA study data has been established in numerous analyses over the years.[7] The present analysis, however, has important limitations. First, the numbers of deaths included in many of the comparisons are small. We have therefore quoted 95% CIs as well as rate ratios. Second, oral contraceptive exposure was judged to have ended by age 45 years for women no longer followed-up individually beyond this

age, and at the age of deletion from the investigation for those in whom detailed follow-up was discontinued for other reasons before that age. This assumption seems unlikely to have introduced important bias. Third, the analysis of the effects of smoking has considered only the amount smoked at recruitment. At that time, 18% of women were light smokers and 14% heavy. Additional data collected from 15 019 of the women around age 45 shows that only 9% were light smokers but 14% were still heavy smokers. These data suggest that we might have underestimated the effects of light smoking. Fourth, information for the whole cohort does not include details of hysterectomy, oophorectomy, age at menopause, or HRT use. Accordingly, we had to assume that the relevant findings in the active cohort apply to the whole cohort. Again, this assumption seems unlikely to have substantially distorted the overall results.

Three other points should be emphasised. First, the findings mainly relate to oral contraceptives containing 50 μg of oestrogen, a high dose by current standards. Such contraceptives have been little used since the early 1980s. Second, some adverse effects of oral contraceptive use, notably the cardiovascular ones, have been shown in other studies to be mainly restricted to current users. Only 16% of the woman-years in our analysis relate to current or recent (within the past year) oral contraceptive use. Third, time relations may be difficult to interpret from mortality data. Thus, oral contraceptives are often stopped when a serious disease (such as ischaemic heart disease) presents, but death might be delayed for many years. In an incidence analysis, such a sequence of events would link the disease to current use, but in a mortality analysis, disease would be related to previous use. Additionally mortality data might be affected by some secondary prevention interventions and by treatment.

We identified no evidence of any harmful effect of oral contraceptive use on mortality from breast cancer. Indeed, our results suggest the reverse, and are consistent with those from the Royal College of General Practitioners (RCGP) study.[8] The Nurses Health study,[9] however, showed increased breast cancer mortality in current oral contraceptive users (rate ratio 1·6, 95% CI 1·1–2·5) but not in past users (1·0, 0·8–1·3). The Collaborative re-analysis Study Group noted the risk of a breast cancer diagnosis to be increased by 24% in current oral contraceptive users, with the risk declining over the 10 years after stopping.[10] Such a small increase in risk, if indeed it applies to mortality, could easily be missed in an investigation the size of the Oxford FPA study. We noted no association between smoking and breast cancer mortality in keeping with a recent report from the US Surgeon General.[6]

In our study, cervical cancer mortality was increased in oral contraceptive users, as in the RCGP study.[8] Data about this disease have not been reported from the Nurses Health study. We have also reported[11] a strong association between long-term oral contraceptive use and cervical cancer incidence in the Oxford FPA study. Findings from investigations that took both sexual behaviour and human papilloma virus infection into account strengthen the hypothesis that oral contraceptives increase the risk of cervical cancer.[12] The (non-significant) association between smoking and mortality from cervical cancer we have found is consistent with the US Surgeon General's report.[6]

Our data indicate a strong protective effect of oral contraceptive use against death from other uterine cancer, although the finding that six of the ten deaths were certified as being from sarcoma was unexpected. A protective effect against mortality from endometrial cancer has also been reported in the RCGP[8] and in the Nurses Health studies.[9] Our findings with respect to smoking are unremarkable: the Surgeon General's report concludes that smoking reduces endometrial cancer mortality in post-menopausal women.[6]

Mortality from ovarian cancer was greatly reduced in users of oral contraceptives. A protective effect of these contraceptives against death from ovarian cancer was also seen in the RCGP study[8] and in the Nurses Health study.[9]

Mortality from melanoma, colorectal cancer, and cancers of the lymphatic and haemopoietic systems were not significantly associated with either oral contraceptive use or smoking. Some researchers have suggested an increased incidence of melanoma[13] and a reduced incidence of colorectal cancer[14] in oral contraceptive users.

We identified no significant relation between oral contraceptive use and lung cancer mortality. As expected,[6] cigarette smoking and mortality from this disease were strongly associated. The (non-significant) association between heavy smoking and mortality from all other cancers is not surprising given the inclusion of cancers of the oesophagus, pancreas, kidney, and bladder in this group.[6]

	Total duration of oral contraceptive use (months)				Number of cigarettes smoked per day			
	Never used	≤48	49–96	≥97	Non-smoker	Ex-smoker	1–14	≥15
Respiratory disease								
Number	18	3	13	14	14	4	6	24
RR	1·0	0·4 (0·1–1·2)	1·1 (0·5–2·3)	1·0 (0·4–2·1)	1·0	1·4 (0·3–4·3)	1·2 (0·4–3·4)	6·4 (3·2–13·4)
Liver, gall-bladder, and pancreas disease								
Number	4	4	3	9	6	0	5	9
RR	1·0	1·9 (0·4–10·0)	1·0 (0·1–5·6)	2·1 (0·6–9·5)	1·0	..	2·8 (0·7–2·2)	6·8 (2·2–23·4)
Accidents and violence								
Number	15	17	6	11	27	4	7	11
RR	1·0	1·9 (0·9–4·1)	0·5 (0·2–1·4)	1·0 (0·4–2·2)	1·0	0·7 (0·2–2·1)	0·8 (0·3–1·9)	1·6 (0·7–3·3)
All other disease								
Number	21	12	12	12	26	6	14	11
RR	1·0	1·0 (0·5–2·2)	0·8 (0·4–1·7)	0·8 (0·3–1·6)	1·0	1·1 (0·4–2·7)	1·7 (0·8–3·3)	1·7 (0·7–3·5)
All deaths								
Number	345	159	172	213	411	88	168	222
RR	1·00	1·00 (0·82–1·21)	0·80 (0·67–0·97)	0·86 (0·72–1·02)	1·00 ..	1·02 (0·80–1·29)	1·24 (1·03–1·49)	2·14 (1·81–2·53)

RR=rate ratio. 95% CIs are shown in parentheses. Oral contraceptive data were adjusted for age, parity, social class, and smoking. Smoking data were adjusted for age, parity, and social class.

Table 4: **Mortality from other causes and all causes in relation to total duration of oral contraceptive use (months) and number of cigarettes smoked per day at entry to the study**

	Cigarettes smoked per day							
	Non-smoker		Ex-smoker		1–14		≥15	
	n	Rate per 1000 w-y	n	Rate per 1000 w-y	n	Rate per 1000 w-y	n	Rate per 1000 w-y
Age (years)								
25–34	14	0·3 (0·2–0·6)	1	0·1 (0·0–0·6)	2	0·2 (0·0–0·5)	4	0·4 (0·1–1·0)
35–44	67	0·8 (0·6–1·0)	8	0·4 (0·2–0·9)	22	0·8 (0·5–1·2)	34	1·5 (1·1–2·1)
45–54	136	1·5 (1·3–1·8)	33	1·8 (1·2–2·5)	62	2·1 (1·6–2·7)	79	3·5 (2·8–4·4)
55 or more	194	3·7 (3·2–4·3)	46	4·3 (3·1–5·7)	82	4·9 (3·9–6·1)	105	8·6 (7·0–10·4)

n=number of deaths. w-y=woman-years. 95% CIs are shown in parentheses. Rates were adjusted for social class.

Table 5: **Mortality from all causes in relation to age and number of cigarettes smoked per day**

Neither the RCGP study nor the Nurses Health study provided much information about mortality from non-reproductive cancers. In the former, however, the rate ratio for lung cancer comparing ever-users of oral contraceptives with never-users was 1·2 (0·8–1·8), whereas the corresponding figure for colorectal cancer was 0·6 (0·4–0·9).

Our findings are consistent with the view that oral contraceptive use increases the risk of fatal ischaemic heart disease.[15] The association, however, is small and not significant. We identified a larger effect in a combined analysis of morbidity and mortality.[16] The effect of heavy smoking in our study is large and similar to that reported by others.[6] Our results suggest that the risk associated with oral contraceptive use is confined to smokers, which is consistent with most other work.[15] Other investigators have usually noted that the increased risk of ischaemic heart disease is restricted to current users.[15] This result is not consistent with our data, but we have already pointed out the difficulty in assessment of time relations in studies of mortality. The RCGP study group[8] did not record a significant increase in mortality from ischaemic heart disease in pill users,[8] although an earlier report, about morbidity and mortality, showed an increased risk largely restricted to smokers, as we have done.[17] Findings in the Nurses Health study have been broadly similar to those in the RCGP study.[9,18]

Mortality from haemorrhagic stroke was slightly (but not significantly) increased in oral contraceptive users. There was no clear relation between fatal haemorrhagic stroke, and duration or recency of contraceptive use. Smoking was strongly related to mortality from this cause as in other studies.[6] An analysis of effects of oral contraceptives within smoking categories did not indicate an interaction. Other studies of haemorrhagic stroke and the contraceptive pill have given variable results, and the existence of an association remains controversial.[19] The latest report from the RCGP study[8] considered all cerebrovascular diseases grouped together; a significant increase in risk of death was recorded in current and recent users (rate ratio 1·9, 1·2–3·1) but there was no increase in risk in women who had stopped using the pill more than 10 years before. The Nurses Health study likewise reported mortality for all cerebrovascular diseases considered together; no significant relations were seen.[9]

Our findings with respect to other stroke (including four deaths from thrombotic stroke) provide no suggestion of any adverse effect of oral contraceptive use. Earlier work from the Oxford FPA study, however, taking into account both morbidity and mortality, showed a clear relation between current and recent oral contraceptive use and thrombotic stroke,[20] as has been shown in most other studies.[21] As indicated above, the RCGP[8] and Nurses Health[9] studies have not provided mortality data separately for different types of stroke.

Mortality from other circulatory diseases showed no relation with oral contraceptive use and a possible moderate increase in heavy smokers. There were no deaths from VTE in our study that could be attributed to oral contraceptive use. That current oral contraceptive use increases the risk of VTE is well-established,[22] and has been clearly demonstrated in a morbidity analysis within the Oxford FPA study.[23] The case fatality rate of VTE is, however, low, and we would not have expected to see more than perhaps one fatal case attributable to oral contraceptive use during the 75 000 woman-years of observation in current and recent users in our study. The RCGP[8] and Nurses Health[9] studies do not provide mortality data for VTE separately, but the former has reported an association between current oral contraceptive use and morbidity from VTE.[24]

None of the disease groups under the heading of other causes showed significant relations with oral contraceptive use. The RCGP study[8] has not provided comparable data save for accidents and violence for which the rate ratio comparing ever-users with never-users was 1·6 (1·1–2·3). A slight, but non-significant, increase in suicide mortality was reported in ever-users in the Nurses Health study (rate ratio 1·3; 0·9–2·0).[9] The strong relation between respiratory disease mortality and smoking was expected.[6] The association between heavy smoking and mortality from diseases of the liver, gallbladder, and pancreas is probably related to alcohol consumption rather than smoking since 11 of the 20 deaths in this category were from alcoholic liver disease.

Overall mortality from all causes in relation to oral contraceptive use in the Oxford FPA study was reassuring. The rate ratio comparing ever-users with never-users was 0·89 (0·77–1·02) and the rate ratios in each of the duration of use groups was less than 1. The overall rate ratio in the RCGP study comparing ever-users with never-users was 1·0 (0·9–1·1) and there was no relationship between duration of oral contraceptive use and overall mortality. Likewise, in the Nurses Health study,[9] the all causes rate ratio comparing ever-users with never-users was 0·93 (0·85–1·01) and again there was no association with duration of oral contraceptive use. Thus we now have the results from three major cohort studies with a total of 5367 deaths and a substantial amount of information about long-term oral contraceptive use which have yielded uniformly reassuring results.

The situation is very different in relation to smoking, especially heavy smoking. The rate ratio for death from all causes for heavy smokers is 2·14 (1·81–2·53) in our study, a figure consistent with that in the Surgeon-General's report.[6] The absolute excess mortality attributable to heavy smoking was 0·7 deaths per 1000 woman-years at ages 35–44; the corresponding figures for ages 45–54 and 55 or more were 2·0 and 4·9, respectively.

The oral contraceptives widely used in the 1970s and early 1980s have now been shown to have no adverse effect on overall mortality in three major cohort studies including many deaths and many women with long-term oral contraceptive use. This is a reassuring finding for many older women today. Although the results should not be extrapolated directly to contemporary low-dose

pills, they do nonetheless offer considerable encouragement. The effects of cigarette smoking, especially heavy smoking, have again been shown to be very harmful, more than doubling mortality from all causes even in young women in the Oxford FPA study. This analysis enables direct contrasts to be drawn between the effects of these two exposures in the same group of women.

Contributors

MV founded the Oxford FPA study in 1968 and has been closely involved with all aspects of its function and analysis to the present time. He took the lead in planning the present set of analyses and wrote the first draft of the report. RP has had responsibility for data management and data calculation in the Oxford FPA study since 1991. She made an important contribution to planning and implementing the analyses and writing the report. DY held the post now occupied by RP until 1991. He rejoined the team as a consultant in 2000 to help develop analytical methods for the present paper and to implement them. He also contributed to writing the report.

Conflict of interest statement

None declared

Acknowledgments

We thank J Winfield, our clinic research assistants, the women taking part in the study, and all the doctors, nurses, and others who have made this study possible.

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